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TOTAL SYNTHESIS OF d,l-OCCIDENTALOL BY PHOTOANNELATION

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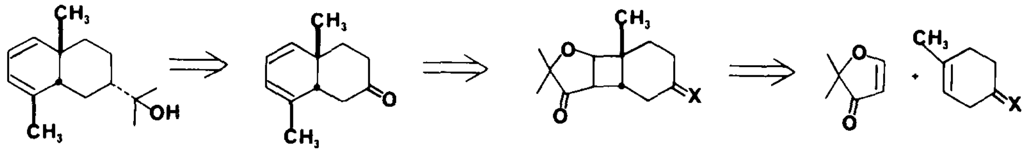
Summary: A nine step synthesis of an intermediate previously used in the synthesis of the sesquiterpene occidentalol is reported which incorporates a 2+2 photocycloaddition reaction as the key carbon carbon bond forming step.

Recent disclosures from these laboratories have described the 2+2 photochemical cycloaddition reaction of alkenes to several different α,β-unsaturated carbonyl compounds with the anticipation that the considerable synthetic potential of the reaction will become better appreciated. At the present time the reaction is regarded by many synthetic chemists more as a curiosity than as a generally useful tool, although the situation is gradually changing.[2] In large measure this pervading mistrust is the result of the multiple stereochemical and regiochemical possibilities which can arise in the reaction as well as an apparent lack of predictability in many cases. Contrary to this opinion, however, it is possible to fashion unsaturated carbonyl photoaddends which are both selective and versatile, and this report is another account of the photochemical reactions of 2,2-dimethyl-3(2H)-furanone (4),[3] one such addend, and the conversion of its photoadducts into useful derivatives.



1 2 3 4 5

Several molecules were targeted to develop the scope of this photoannelation technique. The sesquiterpene occidentalol (1)[4] is one such molecule, the several previously reported syntheses of occidentalol[5] providing a convenient comparison of photoannelation with several other annelation techniques. By this scheme, photoaddition of 4 to an appropriately protected methyl cyclohexene 5 would give a head:tail (HT) adduct 3 suitable for elaboration to racemic occidentalol through the intermediacy of dienone 2. The regiochemistry of the photoaddition step was expected to be largely HT as indicated by previous work. For instance, in a series of three 1-substituted cyclohexenes, the regiochemical ratios (HT:HH) for addition to 4 were 4:1 ($R=CH_3$), 6:1 ($R=C_2H_5$), and 10:1 ($R=CH_2CH_2OAc$)[6]. Moreover, in all cases studied to date the cyclohexane/cyclobutane ring fusion has been cis, assuring correct ring fusion stereochemistry in the final product.

Although the photoaddition of 4 to several derivatives of 4-methylcyclohex-3-enone could be carried out in good yield, the ultimate synthesis of occidentalol incorporated the dithiolane ring (Scheme I).[7] There is little precedent for employing thioketals as protecting groups in photochemical reactions. Berchtold has reported that the carbon-sulfur bond of thioketals undergoes homolysis on irradiation in hydrocarbon solvents to give a variety of products,[9] and other reports describe their dethioketalization on irradiation in ethanol solution containing oxygen.[10]

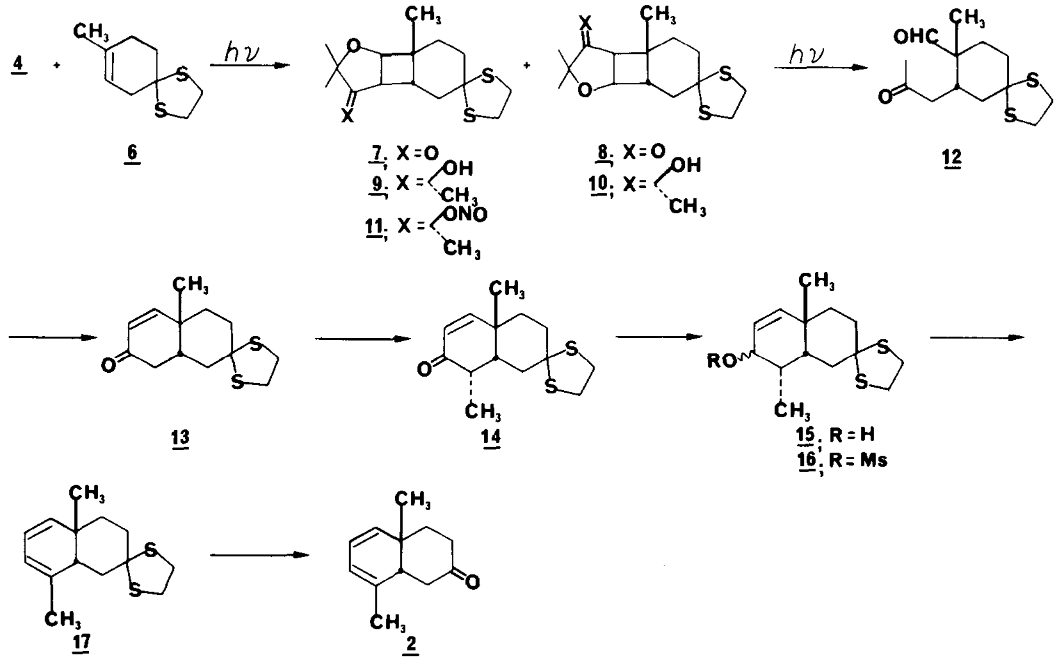
In the event, photoaddition of 4 to 6 in methylene chloride occurred smoothly to give a 67% yield of photoproduct after purification. In hexane only a 34% yield of photoproduct was obtained, presumably because of solubility difficulties. Careful spectroscopic and chromatographic analysis of the crude photoproduct and several of its derivatives revealed it to be a 3.5:1 mixture of regioisomers (HT:HH), in accord with expectations as to orientation of the major isomer, but perhaps lower than might have been expected. However, this ratio is still synthetically useful, particularly given its predictability and the ease of separating regioisomers. Although it was possible to separate these regioisomers chromatographically at this stage, it was more convenient to effect separation after the next reaction.

The elaboration of the photoproduct was accomplished by the oxidative fragmentation procedure recently reported by us for this purpose.[11] Thus, addition of methyl lithium to the furanone carbonyl gave tertiary alcohols 9 and 10. The major alcohol cystalized on trituration with pentane/ether to give a white solid, mp 175-177°, which was homogeneous by spectroscopic and chromatographic analysis. Nitrite ester 11, formed by treatment of 9 with nitrosyl chloride, underwent efficient fragmentation on irradiation to give keto aldehyde 12. The appearance of a sharp aldehyde singlet at $\delta 9.45$ in the NMR spectrum of 12 confirmed that the correct regiochemical assignment had been made. Cyclodehydration of 12 (pTsOH/C_6H_6/reflux) then afforded octalone 13, mp 98-99°, in 70% yield from the photoproduct.[12]

The remainder of the synthesis requires introduction of the secondary methyl group at C4, inclusion of the endocyclic diene moiety, and removal of the thioketal protecting group to give dienone 2. Corey and Watt have previously converted 2 to occidentalol[5g] making its preparation in this work another formal synthesis of the sesquiterpene. Introduction of the methyl group proved to be unduly difficult. Standard alkylation conditions led to none of the desired methylation, often leading to extensive decompostion of the thioketal protective group as a side reaction. Moreover, standard approaches employing activating groups such as the hydroxymethylene derivative were equally unproductive. Eventually it was found that the conditions of Rathke for exhaustive methylation of ketones[13] gave acceptable results. Exposure of a THF solution of 13 to 2.8 equivalents of KH followed by stirring with twenty equivalents of CH_3I for eighteen hours led to a 60% yield of monomethylated ketone 14 along with 40% recovered starting material which could be recycled. The 4 Hz coupling constant of the C-4 methine hydrogen in 14 indicates that the methyl group occupies an α-equatorial position, in accord with expectations. There was no indication in the crude reaction mixture of any dialkylated product, a result which is surprising in light of Rathke´s findings that significantly less severe reaction conditions lead to permethylation of even hindered cyclic ketones.

Introduction of the diene moiety was accompished by an improvement of several literature procedures. Reduction of the ketone with $LiAlH_4$ led to a mixture of the epimeric alcohols 15. Rather than attempt a direct elimination of water as had proved inefficient in previous syntheses of occidentalol,[5a,b,d] 15 was converted to the allylic mesylates 16 by standard procedures, followed by heating at reflux in methylene chloride for three hours to afford homoannular diene 17 in 49% yield for the three steps. Hydrolysis of the thioketal was accomplished without incident by the action of $HgO/HgCl_2$ in aqueous acetonitrile[14] to afford dienone 2 in 77% yield after purification. Although attempts to obtain comparison spectra or an authentic sample of 2 were unsuccessful, all of the assembled data (IR, NMR, MS) are consistent with the assigned structure, thus completing our formal synthesis of d,l-occidentalol.[15]

Scheme I



References and Notes

1. (a) Paper number XV in the series. (b) Financial assistance from the National Institutes if Health (GM 26266) is acknowledged with appreciation.

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7. Photoaddition of 4 to the dimethyl ketal^8 and ethylene ketal of 5 (X=O) also proceeded in good yields (85% and 86%).

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12. Octalone 13 could also be formed from photoproduct 7 by a process initiated by Beckmann fragmentation of the derived oxime as described in S. W. Baldwin and J. M. Wilkinson, Tetrahedron Lett. 2657 (1979).

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15. All new compounds reported herein gave consistent elemental analyses (+0.3%) or correct high resloution mass spectral molecular ions on suitably purified samples as well as consistent spectral data. Yields have not been optimized. Diagnostic information for selected synthetic intermediates includes the following ^{1}H nmr data. (6): δ1.68 (s, 3H), 2.10 (broad m, 4H), 2.60 (broad, 4H), 3.30 (s, 4H), 5.38 (broad s, 1H); (9): δ1.00 (s, 3H), 1.08 (s, 3H), 1.22 (s, 6H), 1.45-1.8 (broad, 2H), 1.95-2.3 (broad, 5H), 2.84 (m, 1H), 3.30 (m, 4H), 3.96 (d, J = 6 Hz, 1H); (13): δ1.28 (s, 3H), 1.7-2.25 (broad, 7H), 2.78 (AB q, J = 4 Hz, 20 Hz, 2H), 3.26 (s, 4H), 5.86 (d, J = 10 Hz, 1H), 6.44 (d, J = 10 Hz, 1H); (14): δ1.03 (d, J = 6.5Hz, 3H), 1.28 (s, 3H), 1.5-2.15 (broad, 7H), 2.82 (dq, J = 6.5 Hz, 4 Hz, 1H), 3.24 (s, 4H), 5.78 (d, J = 10 Hz, 1H), 6.30 (d, J = 10 Hz, 1H); (17): δ0.90 (s, 3H), 1.5-2.3 (broad with s at 1.81, 10H), 3.38 (s, 4H), 5.38 (d, J = 9 Hz), 5.70 (m 1H), 5.92 (dd, J = 5 Hz, J = 9 Hz, 1H); (2): δ0.98 (s, 3H), 1.23 (broad s, 2H), 1.5-2.6 (broad, 8H, including vinyl methyl resonance at 1.77), 5.66 (m, 2H), 6.02 (m, 1H).

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